ORIGINAL ARTICLE

Impact of cardiac resynchronization therapy optimization inside a heart failure programme: a real-world experience

Thibaut Moulin[1], David Hamon[1], Kamila Djouadi[1], Thomas D'Humières[2,3], Nathalie Elbaz[1], Madjid Boukantar[1], Céline Zerbib[1], Ségolène Rouffiac[1], Tarvinder S. Dhanjal[4], Laura Ernande[2], Geneviève Derumeaux[2,3], Emmanuel Teiger[1], Thibaud Damy[1] and Nicolas Lellouche[1]*

[1]*Department of Cardiology, FHU SENEC, AP-HP, University Hospital Henri Mondor, Créteil, France;* [2]*Department of Physiology, FHU SENEC, AP-HP, University Hospital Henri Mondor, Créteil, France;* [3]*INSERM U955, Université Paris-Est Créteil (UPEC), EUR LIVE, Créteil, France; and* [4]*Department of Cardiac Electrophysiology, University of Warwick, Coventry, UK*

Abstract

Aims This study sought to describe and evaluate the impact of a routine in-hospital cardiac resynchronization therapy (CRT) programme, including comprehensive heart failure (HF) evaluation and systematic echo-guided CRT optimization.

Methods and results CRT implanted patients were referred for optimization programme at 3 to 12 months from implantation. The program included clinical and biological status, standardized screening for potential cause of CRT non-response and systematic echo-guided atrioventricular and interventricular delays (AVd and VVd) optimization. Initial CRT-response and improvement at 6 months post-optimization were assessed with a clinical composite score (CCS). Major HF events were tracked during 1 year after optimization. A total of 227 patients were referred for CRT optimization and enrolled (71 ± 11 years old, 77% male, LVEF 30.6 ± 7.9%), of whom 111 (48.9%) were classified as initial non-responders. Left ventricular lead dislodgement was noted in 4 patients (1.8%), and loss or ≤90% biventricular capture in 22 (9.7%), mostly due to arrhythmias. Of the 196 patients (86%) who could undergo echo-guided CRT optimization, 71 (36.2%) required VVd modification and 50/144 (34.7%) AVd modification. At 6 months post-optimization, 34.3% of the initial non-responders were improved according to the CCS, but neither AVd nor VVd echo-guided modification was significantly associated with CCS-improvement. After one-year follow-up, initial non-responders maintained a higher rate of major HF events than initial responders, with no significant difference between AVd/VVd modified or not.

Conclusions Our study supports the necessity of a close, comprehensive and multidisciplinary follow-up of CRT patients, without arguing for routine use of echo-guided CRT optimization.

Introduction

Cardiac resynchronization therapy (CRT) is an effective treatment for heart failure (HF) with reduced left ventricular (LV) ejection fraction (LVEF) and wide QRS complex. Large randomized controlled trials showed that CRT improves symptoms and quality of life, results in favourable LV remodelling and decreases morbidity and mortality in this population.[1,2] However, up to 30% of the implanted patients according to European Society of Cardiology guidelines[3] do not benefit from this therapy and are considered non-responders.[4]

Some common baseline patient characteristics have emerged as risk factors for non-response, such as ischemic cardiomyopathy or non-left bundle branch block (LBBB) QRS

morphology.[5] In addition to rigorous patient selection and optimal LV lead placement, clinicians should strive to find and eliminate potential post-implant causes for non-response, such as inadequate device programming, atrial arrhythmias, premature ventricular contractions (PVCs), secondary valve regurgitation, or non-optimal HF management.[5] In order to improve the rate of CRT responders, post-implantation optimization of atrioventricular and interventricular delays (AVd and VVd) has been proposed. Transthoracic echocardiography is considered the gold standard for AVd and VVd optimization although no consensus has emerged on when, how and which patients should benefit from this technique. Despite promising results on acute haemodynamic parameters, the contrasting results of randomized clinical trials[6,7] led to low use of this time-consuming technique in current practice and last European Heart Rhythm Association position paper states that current evidence does not strongly support the performance of routine AVd and VVd optimization in all patients receiving CRT.[5] However, non-optimal AVd/VVd programming has been shown to be frequent in real-world CRT population,[8] adversely impacting on LV remodelling and outcomes.[9] Echo-guided CRT optimization may therefore still have a place in the management of CRT patients inside a comprehensive CRT and HF programme.[5,10] Few data are available on the impact of such programme in contemporary unselected real-life CRT population.[8]

Our study aimed to describe and evaluate the impact on CRT response of a routine in-hospital CRT management programme, including HF clinical and biological status and systematic echo-guided CRT optimization.

Methods

Patient population

Between March 2015 and October 2019, all CRT-implanted patients at Henri Mondor University Hospital (AP-HP, Creteil, France), according to European Class I or IIa recommendations,[3] were referred for optimization programme at 3 to 12 months after the index procedure. Inclusion criteria were all patients implanted with CRT-pacemaker or CRT-defibrillator admitted for CRT optimization management. Exclusion criteria were missing functional status (NYHA class) at implantation and interval between first CRT implantation and optimization ≥1 year.

Implantation procedure

Patients were implanted with commercially available devices (Boston Scientific, Medtronic, St Jude Medical or Liva Nova) and any compatible right atrial, right ventricular (RV) and LV lead. LV stimulation vectors and initial AVd and VVd were programmed at the discretion of the implanting physician. Intracardiac electrogram (IEGM)-based optimization algorithms QuickOpt™ (Abbott, Chicago, Illinois, USA) and SmartDelay™ (Boston Scientific, Marlborough, Massachusetts, USA) were used for St Jude Medical and Boston Scientific devices respectively when deemed necessary. AdaptiveCRT™ algorithm (Medtronic, Minneapolis, Minnesota, USA) for dynamic IEGM-based optimization could be activated for compatible Medtronic devices.[11] For CRT defibrillators from Liva Nova, SonR™ algorithm (Sorin Microport CRM, Clamart, France) for continuous AVd/VVd optimization based on peak endocardial acceleration, was activated when the appropriate right atrial lead was implanted.[12] Eligible patients were systematically referred at 3 to 12 months after CRT implantation for comprehensive optimization programme.

Comprehensive evaluation and optimization procedure

Patients were hospitalized for 1 or 2 days. The assessment systematically included clinical evaluation, 12-lead electrocardiogram (ECG), 6 min walk test to assess exercise tolerance, Minnesota Living with Heart Failure Questionnaire to assess quality of life, antero-posterior chest X-ray, standard laboratory tests and a comprehensive device analysis. Next, transthoracic echocardiography (Vivid E95, GE Medical Systems, Milwaukee, USA) was performed by an expert physician and evaluated: LV diameters and volumes, LVEF measured by Simpson Biplane method, left ventricular outflow tract (LVOT) velocity time integral (VTI), LV filling pattern with mitral pulsed Doppler, systolic pulmonary artery pressure, and interventricular mechanical delay calculated as the difference between LV and RV pre-ejection period in absolute value (measured from the onset of QRS to onset of aortic and pulmonary flows respectively).[13] Finally, an echo-guided optimization of AVd and VVd was systematically sought except for patients who had recovered LVEF ≥60% with initial settings, and patients with SonR™ algorithm activated. For patients in sinus rhythm (SR), AVd optimization was first achieved according to the mitral pulsed Doppler based iterative method.[13] When feasible, atrial-paced (AP) and atrial-sensed (AS) AVd were independently optimized. Otherwise, an empirical AP-AS AVd offset was programmed. Next, for all patients including those in atrial fibrillation (AF), VVd optimization was performed with 10 ms steps from 50 ms LV-first to 50 ms RV-first in order to obtain the largest LVOT VTI.[13] In case of hesitation between two LVOT VTI-optimized VVd, physician could choose the one with the lowest interventricular mechanical delay. In case of non-optimal LV filling pattern and/or LVOT VTI, patients with AdaptiveCRT™ algorithm 'ON' could be switched to optimized fixed settings. Several physicians and sonographers were

trained in the standardized optimization protocol. All CRT optimization procedures were supervised by a single research engineer trained in cardiac pacing.

Evaluation of initial cardiac resynchronization therapy response

At the time of in-hospital optimization, CRT initial response was assessed using a clinical composite score (CCS).[14] A patient was considered a CRT responder if (i) had no hospitalization for decompensated HF and (ii) had ≥1-point decrease in New York Heart Association (NYHA) functional class since CRT implantation.

Follow-up

We prospectively evaluated the clinical impact of our CRT optimization programme. Primary endpoint was the rate of CCS improvement at 6 months post-optimization. Precisely, a patient was considered improved since optimization if (i) alive; (ii) had no hospitalization for decompensated HF, heart transplantation or need for mechanical circulatory support; and (iii) had ≥1-point decrease in NYHA class since optimiza-

Figure 1 Flow chart of the CRT optimization programme. CRT, cardiac resynchronization therapy; ECG, electrocardiogram; LVEF, left ventricle ejection fraction; AVd, atrioventricular delay; VVd, interventricular delay; LVOT VTI, left ventricular outflow tract velocity time integral.
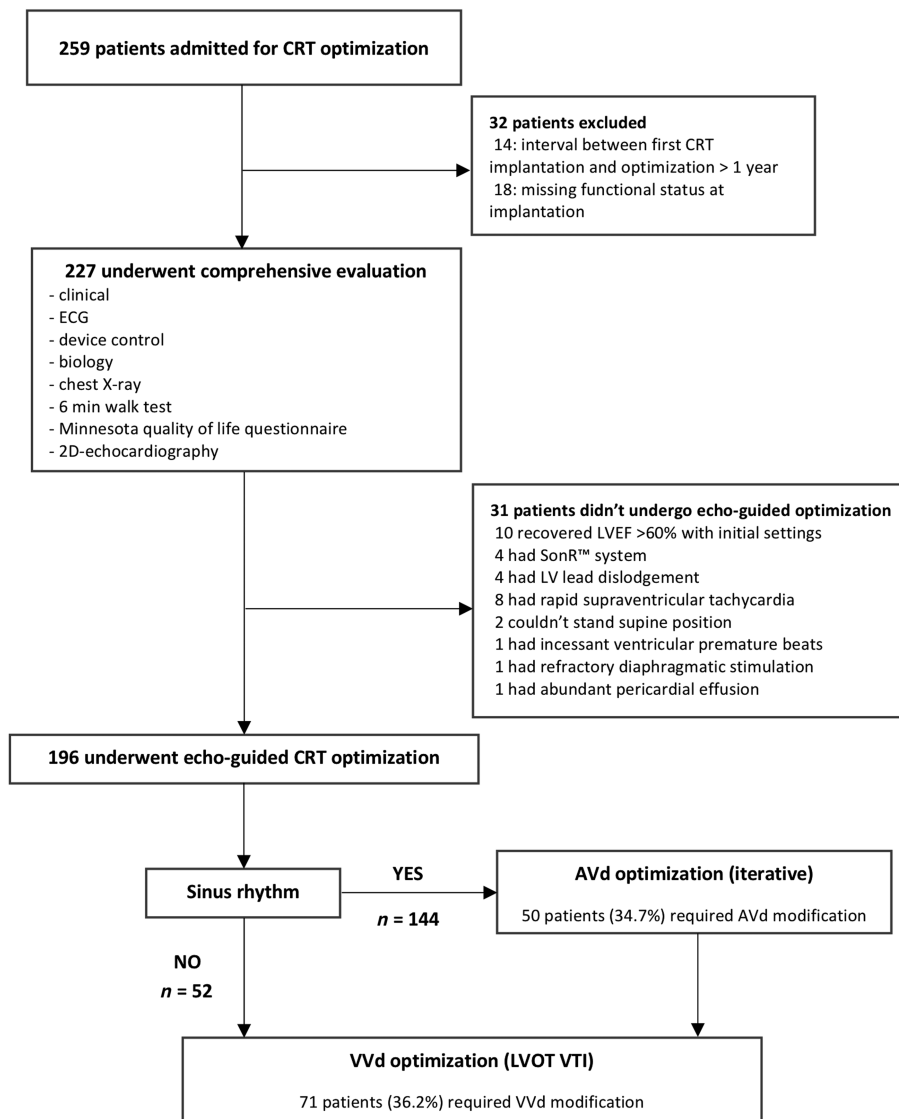
tion. Secondary endpoints included NYHA class and a combined endpoint of hospitalization for decompensated HF, all-cause death, heart transplantation and need for mechanical circulatory support after optimization programme.

The CCS at 6 months post-optimization was ascertained during in-person visit. All case report forms were monitored prospectively by an independent research technician. Data during the follow-up were collected from paper medical reports, clinic consultation and all patients received a phone call from our unit every 3 months to evaluate their clinical status and assess potential hospitalization due to decompensated HF.

The study protocol was approved by a national ethics committee and the study was performed in accordance with the ethical principles stated in the Declaration of Helsinki. All patients gave written inform consent to participate to the study.

Statistical analysis

Continuous variables are expressed as mean ± SD. They were compared using the unpaired Student's t-test or Mann–Whitney test if necessary. Categorical variables, expressed as numbers or percentages, were analysed with the χ^2 or Fisher's exact test. Univariate comparisons of these variables were performed. Kaplan–Meier survival curves were constructed for the combined endpoint. Log-rank test was used to compare the cumulative probability of event curves between groups. All tests were two-tailed and a P-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc and R v3.6.0 (R Foundation, Vienna, Austria; package cutpoint).

Results

Patient population

Between September 2015 and February 2020, 259 patients were admitted in Henri Mondor University Hospital (AP-HP, Creteil, France) for CRT optimization programme. NYHA class at implantation was missing for 18 patients and 14 patients were excluded due to an interval between first CRT implantation and optimization superior to 1 year (*Figure 1*). A total of 227 patients were included. Median time between implantation and CRT optimization programme was 5.4 months (interquartile range 3.8–7.5 months).

Table 1 Baseline characteristics at CRT implantation

	N = 227
Age, year	71.4 ± 11.5
Male sex, *n* (%)	174 (76.7)
Body mass index, kg/m^2	27 ± 5.4
Cardiopathy	
Ischaemic cardiomyopathy, *n* (%)	83 (36.6)
Non-ischaemic cardiomyopathy, *n* (%)	83 (36.6)
Other, *n* (%)	61 (26.9)
Co-morbidities	
Diabetes, *n* (%)	72 (31.7)
Hypertension, *n* (%)	143 (63.0)
Dyslipidaemia, *n* (%)	113 (49.8)
Chronic kidney disease, *n* (%)	109 (48.0)
Obesity, *n* (%)	51 (22.5)
NYHA class	
II, *n* (%)	103 (45.4)
III, *n* (%)	90 (39.6)
IV, *n* (%)	34 (15.0)
Atrial fibrillation, *n* (%)	123 (54.2)
Paroxysmal	47 (20.7)
Persistent	30 (13.2)
Permanent	46 (20.3)
NT-proBNP, pg/mL	4809 ± 6821
ECG	
Spontaneous QRS, *n* (%)	175 (77.1)
QRS duration, ms	138.5 ± 28.0
Complete LBBB, *n* (%)	128 (56.4)
RV pacing, *n* (%)	52 (22.9)
QRS duration, ms	167.7 ± 31.6
Echocardiography	
LVEF, %	30,6 ± 7.9
LVEF >35%, *n* (%)	45 (19.8)
LV end-diastolic diameter, mm	61.3 ± 12.1
LV end-diastolic volume, mL	176.9 ± 84.6
Medication, *n* (%)	
Beta-blocker	184 (81.2)
ACE inhibitor or ARB	170 (74.9)
ARNI	30 (13.2)
Aldosterone antagonist	123 (54.2)
Diuretic agent	181 (79.7)
Amiodarone	67 (29.5)
Device data	
CRT defibrillator, *n* (%)	150 (66.1)
LV lead position, *n* (%)	
Lateral	114/201 (56.7)
Anterolateral	52/201 (25.9)
Posterolateral	24/201 (11.9)
Anterior	4/201 (2.0)
Posterior	2/201 (1.0)
Left Bundle Branch	1/201 (0.5)
Epicardial	3/201 (1.5)
Quadripolar LV lead, *n* (%)	187 (87.8)
Boston Scientific device, *n* (%)	74 (32.6)
St Jude Medical device, *n* (%)	68 (30.0)
Medtronic device, *n* (%)	63 (27.8)
LivaNova device (only CRT-D), *n* (%)	22 (9.7)
Remote monitoring, *n* (%)	36 (15.9)

Continuous variables are expressed using mean ± SD.
ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RV, right ventricular.

Baseline characteristics

Baseline characteristics of the 227 patients at CRT implantation are presented in *Table 1*. Particularly, 77% of patients were male with a mean age of 71 ± 11 years and 37% presented ischemic cardiomyopathy. Forty-five per cent of patients were in NYHA functional class II. Mean LVEF was 30.6 ± 7.9%. Mean native QRS duration was 138.5 ± 28 ms (median 140 ms), and 56% had complete LBBB while 23% underwent CRT upgrade from prior RV pacing. A total of 42 patients (18.5%) were implanted according to the Class I recommendation as follows: LVEF ≤35%, QRS ≥ 150 ms, LBBB morphology, NYHA class ≥2, SR.[3] Remote monitoring was activated for 16% of our population.

Initial cardiac resynchronization therapy response

At the time of CRT optimization, according to the CCS, 116 patients (51.1%) were classified as CRT responders. Characteristics of CRT responders versus non-responders are presented in *Table 2*. Non-responders were older, had more ischemic cardiomyopathy and other comorbidities such as chronic renal failure and hypertension. CRT responders had narrower LV-captured QRS complex than non-responders (132.1 ± 22.7 ms vs. 140.2 ± 25.8 ms, $P = 0.01$). Other differences were not statistically significant.

Comprehensive evaluation and screening for potential causes of cardiac resynchronization therapy non-response

Between implantation and optimization, mean NYHA class improved by 0.65 ± 0.94. Mean LVEF was 38.7 ± 11% and mean LV-captured QRS duration was 136.1 ± 24.5 ms at optimization time (Supporting Information, *Table S1*). Screening for potential causes of CRT non-response is presented in *Figure 2*. Particularly, 6 patients (2.6%) presented with no LV capture due to LV lead dislodgement or high LV stimulation threshold, and 20 patients (8.8%) presented with BiV pacing rate ≤90% (see management details in online-only

Table 2 Characteristics of initial CRT responders versus non-responders

	Responders (N = 116)	Non-responders (N = 111)	P
Baseline characteristics			
Age, year	69.4 ± 11.3	73.6 ± 11.5	0.006
Male sex, n (%)	90 (77.6)	84 (75.7)	0.73
Body mass index, kg/m^2	26.9 ± 5.4	27.2 ± 5.9	0.69
Ischaemic cardiomyopathy, n (%)	32 (27.6)	51 (45.9)	0.004
Non-ischaemic cardiomyopathy, n (%)	53 (45.7)	30 (27.0)	0.004
Cardiac amyloidosis, n (%)	6 (5.2)	12 (10.8)	0.12
Diabetes, n (%)	36 (31.0)	36 (32.4)	0.82
Hypertension, n (%)	65 (56.0)	78 (70.3)	0.03
Dyslipidaemia, n (%)	53 (45.7)	60 (54.1)	0.21
Chronic kidney disease, n (%)	48 (41.4)	61 (55.0)	0.04
Obesity, n (%)	24 (20.7)	27 (24.3)	0.51
NYHA class at implantation	2.82 ± 0.72	2.57 ± 0.70	0.009
NT-proBNP at implantation, pg/mL	5013 ± 8231	4596 ± 4834	0.64
History of atrial fibrillation, n (%)	62 (53.4)	61 (55.0)	0.82
Permanent atrial fibrillation, n (%)	19 (16.4)	27 (24.3)	0.14
QRS duration before implantation, ms	147.4 ± 32.0	141.8.6 ± 30.0	0.18
LBBB, n (%)	70 (60.3)	58 (52.3)	0.22
RV pacing before implantation, n (%)	24 (20.7)	28 (25.2)	0.42
LVEF at implantation, %	30.4 ± 8.6	30.8 ± 7.1	0.70
LV end-diastolic diameter at implantation, mm	62.7 ± 29.3	59.7 ± 29.6	0.44
LV end-diastolic volume at implantation, mL	189.2 ± 112.7	162.4 ± 95.1	0.055
CRT Defibrillator, n (%)	75 (64.7)	75 (67.6)	0.64
Lateral LV lead, n (%)	63/103 (61.2)	51/98 (52.0)	0.19
Remote monitoring, n (%)	17 (14.7)	19 (17.1)	0.61
CRT initial settings (at optimization time)			
AP AVd, ms (n = 164)	163 ± 27.6	158.6 ± 29.8	0.25
AS AVd, ms (n = 164)	119.6 ± 26.0	114.7 ± 21.6	0.12
VVd = 0 ms, n (%)	84/108 (77.8)	84/108 (77.8)	1.00
LV first pacing, n (%)	16/108 (14.8)	14/108 (13.0)	0.69
RV first pacing, n (%)	0/108 (0)	5/108 (4.6)	0.12
LV only pacing, n (%)	6/108 (5.6)	3/108 (2.8)	0.31
AdaptiveCRT™ 'ON', n (%)	18/31 (58.1)	16/32 (50.0)	0.52
QRS duration, ms	132.1 ± 22.7	140.2 ± 25.8	0.01

Continuous variables are expressed using mean ± SD.
CRT, cardiac resynchronization therapy; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RV, right ventricular; AP, atrial-paced; AS, atrial-sensed; AVd, atrioventricular delay; VVd, interventricular delay.

Figure 2 Screening for potential causes of CRT non-response. AVd, atrioventricular delay; VVd, interventricular delay; LV, left ventricular; HF, heart failure; BiV, biventricular; SVT, supraventricular tachycardia; PVC, premature ventricular contraction.
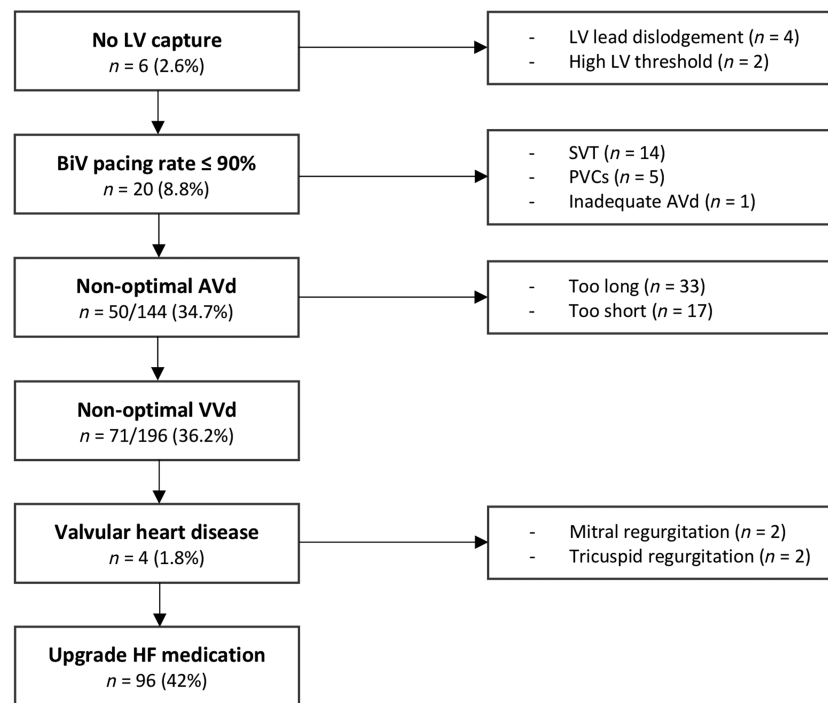
supplementary data). Phrenic nerve stimulation was noted in 9 patients (4%), successfully corrected with vector configuration modification in 8. Nineteen patients (8%) presented with decompensated HF and required prolongation of hospitalization for intravenous diuretic administration. Upgrade of HF medication, defined as introduction or increase of either beta-blocker, aldosterone antagonist, angiotensin conversion enzyme inhibitor, angiotensin receptor blocker, angiotensin receptor neprilysin inhibitor or diuretics occurred in 96 patients (42%).

Atrioventricular delay and interventricular delay optimization

Among the 227 patients, 10 recovered LVEF ≥60% with initial settings, 4 had SonR™ algorithm activated, and 17 could not undergo echo-guided CRT optimization for various reasons (see *Figure 1*). In total, 196 patients (86.3%) underwent echo-guided AVd and VVd optimization.

Of the 144 patients in SR, 50 (34.7%) required ≥10 ms AVd modification (reduction for two third, prolongation for one third, mean change 35.6 ± 23 ms, Supporting Information, *Table S2*). Distributions of AS AVd before and after optimization are presented in *Figure 3*. Echo-guided optimization resulted in a global reduction of AVd.

Of the 196 patients, 71 (36.2%) required ≥10 ms VVd modification (mean change 21.3 ± 10.2 ms), among which 50 (70.4%) required change from synchronous BiV pacing (VVd = 0 ms) to sequential LV first pacing (Supporting Information, *Table S3*). After optimization, 105 of the 196 patients (53.6%) presented synchronous BiV pacing and 85 (43.4%) presented sequential LV first pacing (*Figure 3*).

In total, 91 of the 196 patients (46.4%) required ≥10 ms AVd and/or VVd echo-guided modification, and 30 (20.8% of patients in SR) required both. Examples of echo-guided optimization of AVd and VVd are presented in *Figure 4*.

Among initial CRT responders, 28 patients (35.0%) required AVd modification and 43 (41.0%) required VVd modification, versus 22 (34.4%) and 28 (30.8%) among initial non-responders (AVd: *P* = 0.94; VVd: *P* = 0.14).

Of the 35 patients with AdaptiveCRT™ algorithm 'ON', 14 (40.0%) were switched to optimized fixed AVd/VVd. The QuickOpt™ proposal matched with the echo-based optimized AVd in four patients (10.0%) and the VVd in four patients (6.8%), while the SmartDelay™ proposal matched with the echo-based optimized AVd in two patients (3.8%).

Follow-up

Clinical status at 6 months post-optimization was obtained for 208 patients (91.6%) while 19 (8.4%) were lost to

Figure 3 Distribution of AVd and VVd before and after optimization. (A) AS AVd before optimization. (B) AS AVd after optimization. (C) VVd before optimization. (D) VVd after optimization. AVd, atrioventricular delay; AS, atrial-sensed; LV, left ventricular; RV, right ventricular; VVd, interventricular delay.
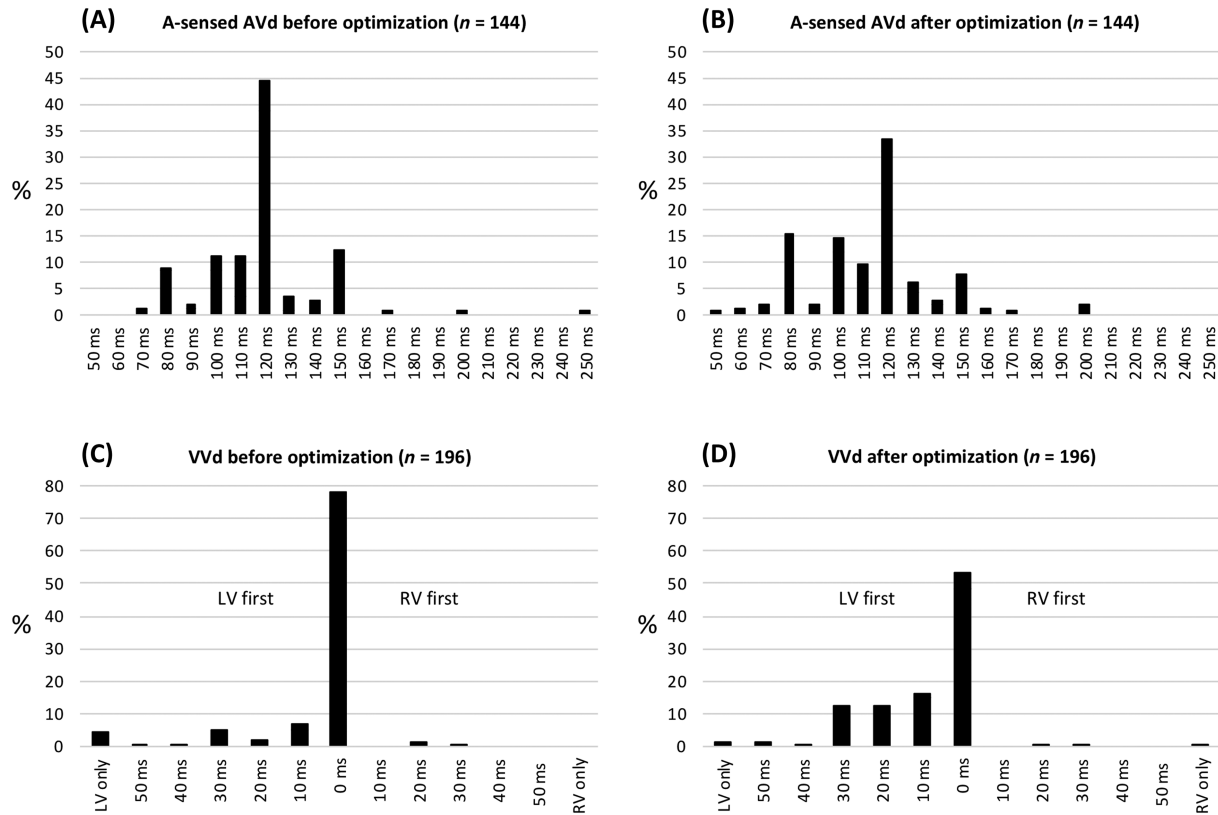
follow-up. Since optimization, 42 patients (20.2%) were considered CCS improved, while 57 (27.4%) were considered worsen among which 13 (6.3%) died, and 22 (10.6%) were hospitalized for decompensated HF before 6 months revaluation. Importantly, 36 of the 105 (34.3%) initial non-responders were CCS improved 6 months after our programme (*Figure 5*). Between optimization and 6 months revaluation, mean NYHA class improved by 0.08 ± 0.70 points among all 6 months survivors (*n* = 195) and by 0.32 ± 0.74 points among initial non-responders (*n* = 96).

Characteristics of 6 months-improved versus not improved patients among initial CRT non-responders are presented in *Table 3*. Improved patients had higher NYHA class, higher 6 min walk test distance, and less dilated LV at optimization time. No other statistical difference was noted between the two groups. Importantly, neither echo-guided AVd nor VVd modification was associated with CCS improvement after the optimization programme (*Table 3*).

After 1-year follow-up from optimization, the combined endpoint of hospitalization for decompensated HF, all-cause death, heart transplantation or need for mechanical circula-tory support occurred in 36 patients (17.3%). The cumulative rate of the combined endpoint during the year following optimization was compared between initial CRT responders and non-responders. Non-responders maintained a higher rate of major HF events (25.7% vs. 8.7%, $P < 0.01$) (*Figure 6A*), and this rate was not modified by AVd/VVd optimization in initial non-responders (*Figure 6B,C*).

Discussion

We present a cohort of real-life systematic comprehensive in-hospital CRT management programme including routine echo-guided AVd and VVd optimization. The main findings of our study are (i) 46% of patients required echo-guided modification of AVd and/or VVd (AVd: 35%, VVd: 36%); (ii) 34% of the initial CCS non-responders were CCS improved 6 months after the programme; (iii) neither AVd nor VVd echo-guided modification was significantly associated with CCS improvement at 6 months post-optimization.

Figure 4 Examples of echo-guided AVd and VVd optimization. (A, B) 78-year-old patient with non-ishemic cardiomyopathy and complete AV block, implanted with CRT pacemaker. (A) Too long initial AS AVd (150 ms) with merged E and A waves. (B) Shortening the delay to 80 ms resulted in separation of (E) and (A). (C, D) 71-year-old patient with valvular cardiopathy and sinus node dysfunction, implanted with CRT defibrillator. (C) Too short initial AP AVd (120 ms) with truncated A wave. (D) After extension of AP AVd to 160 ms, mitral closure click was aligned with end of A wave. (E, F) 59-year-old patient with ischemic cardiomyopathy, complete LBBB and LVEF reduced to 25%, implanted with CRT defibrillator. Changing the VVd from 10 to 30 ms (LV first) resulted in an acute increase of LVOT VTI (12.3 cm to 16.8 cm, heart rate 65 b.p.m.). AVd, atrioventricular delay; AS, atrial-sensed; AP, atrial-paced; CRT, cardiac resynchronization therapy; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; VTI, velocity time integral; VVd, interventricular delay.
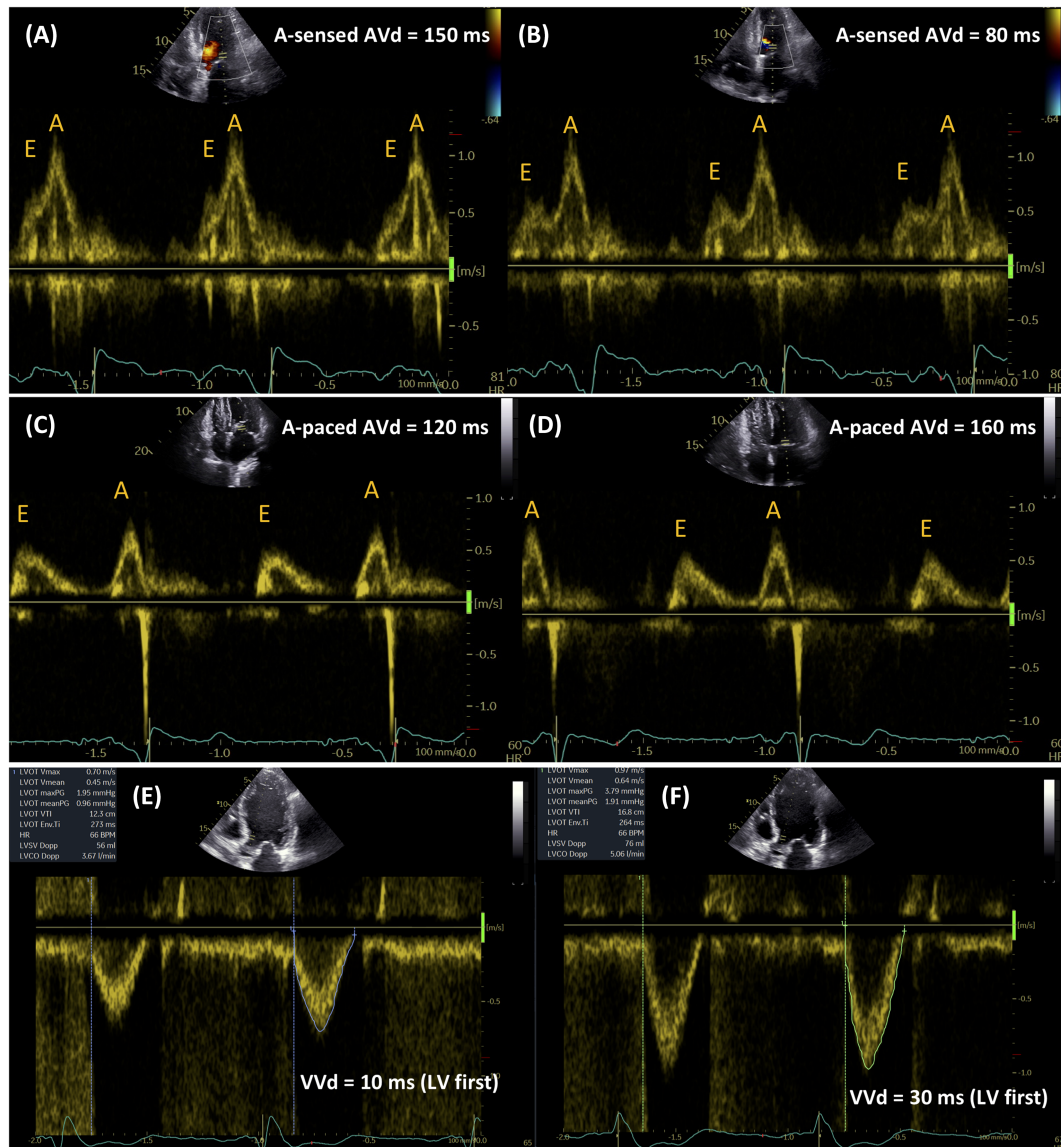
Cardiac resynchronization therapy response

CRT is a highly effective treatment for HF, but a significant proportion of non-response has remained its main limitation. Yet, no consensus definition of CRT response has emerged, and the rate of non-responders highly depends on its definition.[4] The CCS used in our study was validated in landmark CRT trials.[4]

In a recent real-life prospective study using this composite endpoint, the rate of non-responders at 6 months reached 31%.[15] This rate was significantly higher in our population (49%) and several reasons may explain this discrepancy. First, our population was older (71.4 vs. 67.5 years old). Furthermore, our patients were mildly symptomatic at implantation (45% NYHA II) and therefore less likely to improve their

Figure 5 Evolution of functional status according to the clinical composite score (CCS). CRT, cardiac resynchronization therapy.
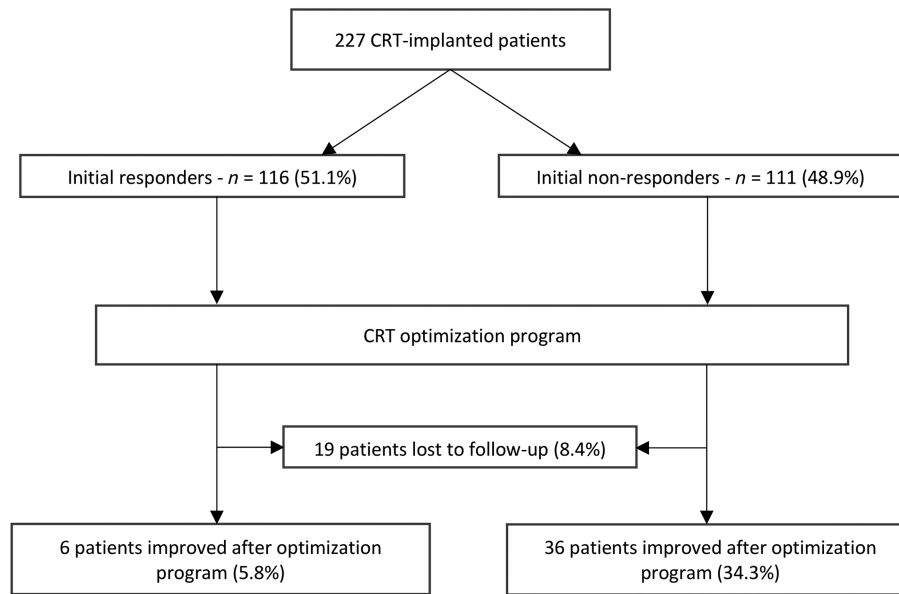
functional status. Consistent with the former study, we emphasize that CRT in real-world practice is used in a wider range of patients than enrolled in randomized CRT trials, such as non-LBBB QRS morphology, NYHA II, LVEF >35%, candidates for AV junction ablation due to uncontrolled heart rate in AF, upgrade from conventional RV pacing, or expected high percentage of RV pacing.[15] Only a minority of patients were implanted according to Class I recommendation (LVEF ≤35%, QRS ≥ 150 ms, LBBB morphology, NYHA class ≥2, SR) which may explain the low observed rate of initial CRT-reponse.

Atrioventricular delay optimization

Rational for AVd optimization lies in allowing the maximal LV diastolic filling time, preventing a too long interval resulting in a fusion between passive and active filling, and a too short interval resulting in truncated active filling. Nevertheless, routine post-implantation echo-guided AVd optimization was not superior compared with an empirical fixed AS AVd of 100–120 ms in a randomized study.[6] Other authors suggest that AVd optimization could have a beneficial impact in selected non-responder CRT patients: in a clinical study of 75 CRT non-responders, inadequate AVd were found to account for non-response in almost half of patients in whom ≥30 ms echo-guided AVd modification resulted in significant clinical improvement.[10] In our study, 35% of patients in SR had non-optimal AVd with initial real-life settings, without difference between initial responders and non-responders, and neither ≥10 ms nor ≥30 ms echo-guided AVd modification in initial non-responders was associated with clinical im-

provement at follow-up. In Mullen's study, referral of non-responder patients was based on the referring physicians' clinical impression which might have selected patients who were more prone to be successfully optimized.[10] Our results suggest a much lower clinical impact of such an intervention in an unselected CRT population compared with other modifiable causes of non-response. The wide use of device-based algorithms for optimal AVd +/− VVd in current clinical practice may also have reduced the impact of echo-based optimization in our contemporary CRT population.

Interventricular delay optimization

Rational for VVd optimization lies in improving RV-LV synchrony in order to maximize stroke volume and cardiac output. In our study, 36% of patients had non-optimal VVd with initial settings. Most of them (70%) had initial synchronous BiV pacing and were programmed with sequential LV first pacing. Distribution of optimized VVd was comparable to that of the controlled INSYNC III trial with almost 50% of patients programmed in sequential LV first pacing (*Figure 3*).[16] Early studies showed that VVd optimization may improve LV stroke volume, LVEF and reduce mitral regurgitation compared with simultaneous BiV pacing[17] which was not translated into significant clinical improvement in larger controlled trials.[16] In the randomized RHYTHM II study, VVd optimization did not improve LVEF or LV volume at 6 months compared with out of the box simultaneous BiV pacing.[7] Data on the clinical impact of VVd optimization in initial

Table 3 Characteristics of CCS improved versus not improved patients at 6 months follow-up, among initial CRT non-responders

	Improved (N = 36)	Not improved (N = 69)	P
Interventions at optimization			
AVd and/or VVd modification ≥ 10 ms, n (%)	12/24 (50)	23/62 (37.1)	0.28
AVd modification ≥ 10 ms, n (%)	5/17 (29.4)	14/44 (31.8)	0.86
AVd modification ≥ 30 ms, n (%)	1/17 (5.9)	10/44 (22.7)	0.12
VVd modification ≥ 10 ms, n (%)	10/24 (41.7)	16/62 (25.8)	0.15
VVd modification ≥ 20 ms, n (%)	4/24 (16.7)	6/62 (9.7)	0.36
AVd and VVd modification ≥ 10 ms, n (%)	3/17 (17.6)	7/44 (15.9)	0.87
≥10% acute increase of LVOT VTI, n (%)	5/24 (20.8)	11/61 (18)	0.76
Characteristics at optimization			
NYHA class	2.81 ± 0.67	2.49 ± 0.60	0.01
Minnesota QOL HF score, points	34.9 ± 25.1 (n = 28)	37.1 ± 22.6 (n = 60)	0.68
6 min walk test, m	369 ± 114 (n = 22)	290 ± 125 (n = 45)	0.01
LVEF, %	37.2 ± 11.9	35.2 ± 11.2	0.40
LV end-diastolic diameter, mm	61 ± 27.1	60.2 ± 9.5	0.83
LV end-diastolic volume, mL	147.3 ± 53.5	178.1 ± 80	0.04
AS AVd after optimization, ms	113.6 ± 21.9 (n = 22)	113.7 ± 25.0 (n = 47)	1.00
AP AVd after optimization, ms	154.1 ± 33.6 (n = 22)	152.0 ± 37.3 (n = 47)	0.86
VVd = 0 ms after optimization, n (%)	19 (52.8)	40 (58.0)	0.61
LV first pacing after optimization, n (%)	12 (33.3)	23 (33.3)	1.00
Baseline characteristics			
Age, year	72.4 ± 14.6	74.4 ± 10.0	0.41
Male sex, n (%)	26 (72.2)	56 (81.2)	0.29
Body mass index, kg/m²	26.7 ± 5.2	27.5 ± 6.3	0.51
Ischaemic cardiomyopathy, n (%)	14 (38.9)	33 (47.8)	0.38
Non-ischaemic cardiomyopathy, n (%)	10 (27.8)	19 (27.5)	0.98
Diabetes, n (%)	9 (25.0)	22 (31.9)	0.46
Hypertension, n (%)	26 (72.2)	49 (71.0)	0.90
Dyslipidaemia, n (%)	18 (50.0)	38 (55.1)	0.62
Chronic kidney disease, n (%)	21 (58.3)	35 (50.7)	0.46
Permanent atrial fibrillation, n (%)	10 (27.8)	15 (21.7)	0.49
QRS duration at implantation, ms	135.6 ± 31.0	137.7 ± 26.5	0.72
Complete LBBB, n (%)	17/23 (73.9)	36/63 (67.9)	0.16
RV pacing before CRT implantation, n (%)	12 (33.3)	14 (20.3)	0.14
CRT defibrillator, n (%)	25 (69.4)	46 (66.7)	0.77
Lateral LV lead, n (%)	14/28 (50.0)	33/64 (51.6)	0.89
Remote monitoring, n (%)	5 (13.9)	14 (20.3)	0.42

Continuous variables are expressed using mean ± SD.
AVd, atrioventricular delay; VVd, interventricular delay; AS, atrial-sensed; AP, atrial-paced; LVOT VTI, left ventricular outflow tract velocity time integral; CRT, cardiac resynchronization therapy; HF, heart failure; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction.

Figure 6 Cumulative rate of major HF events (HF hospitalization, all-cause death, heart transplantation, mechanical circulatory support) after optimization programme (1 year follow-up). Kaplan–Maier curves for (A) initial CRT responders versus non-responders; (B) initial CRT non-responders AVd modified versus AVd non-modified; (C) initial CRT non-responders VVd modified versus VVd non-modified. AVd, atrioventricular delay; CRT, cardiac resynchronization therapy; HF, heart failure; VVd, interventricular delay.
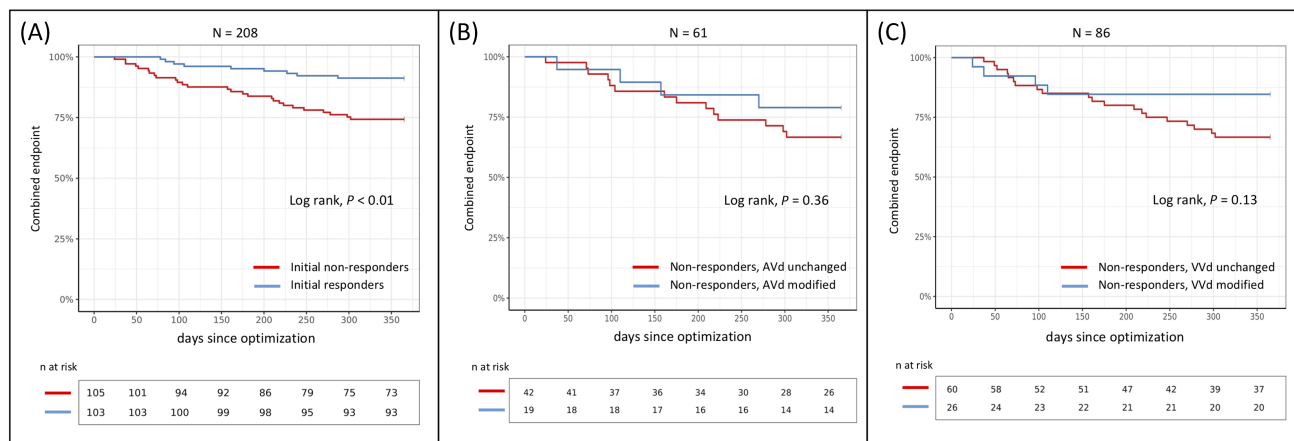
CRT non-responders are particularly scarce. In the RESPONSE-HF trial, CRT non-responders at 3 months were randomized to VVd optimization vs. simultaneous BiV pacing. In the VVd optimization group, more patients became responders at 9 months, but this difference did not reach statistical significance and results were only published in abstract form.[18] Among initial non-responders from our real-life study, the rate of CCS improvement at 6 months from optimization as well as the rate of major HF events were not statistically different between VVd modified patients and those with already optimal VVd. Although possibly due to a lack of power, these results suggest that the magnitude of acute haemodynamic effect with optimized VVd may be too small to be clinically meaningful in long term follow-up. Indeed, echo-guided modification of VVd led to a modest acute increase of LVOT VTI and therefore stroke volume (8.6%, Supporting Information, *Table S3*).

Limits of cardiac resynchronization therapy optimization

Echo-based AVd and VVd optimization present inherent limits. First, the technical difficulty of the methods may generate inter-observer variability, which was not analysed in our study. Second, the heterogeneity of real-life CRT patients (multiple device brands, automatic algorithms, significant part of patients in AF or with high rate of atrial pacing) makes the development of a routine standardized optimization protocol challenging. Finally, optimal AVd and VVd have been shown to vary over time according to LV (reverse) remodelling, load conditions, and exercise, which led some authors to question the relevance of fixed optimized delays.[19] However, frequent periodic echo-guided AVd/VVd optimization may not be feasible in daily clinical practice. In this context, automatic and continuous device-based optimization using IEGM or peak endocardial acceleration, which have been shown to be at least non-inferior to echo-based methods are attractive but their impact on outcomes compared with fixed settings must be further evaluated.[11,12]

Based on our results, we cannot exclude that some selected patients may take advantage of echo-guided AVd/VVd optimization, however, our study lacks the power to perform such subgroup analyses.

Comprehensive cardiac resynchronization therapy management programme

Our study confirms the necessity of a close, comprehensive and multidisciplinary follow-up of CRT patients.[5] Indeed, a significant part of them presented with LV lead complication, loss/infrequent BiV capture or arrhythmia. However, this high rate must be put into perspective by the small number of patients with remote monitoring in our study population. Our programme allowed the titration of HF medication in a significant proportion of patients. Finally, although echo-guided CRT optimization had low impact on outcomes, 36% of initial non-responders experienced CCS improvement secondary to our programme. Nevertheless, as described by other author, even after comprehensive management, initial CCS non-responders maintained a higher rate of major HF events at follow-up.[15]

Study limitations

This study has several limitations. First, even if we prospectively evaluated our strategy of CRT optimization on a large cohort of patients, no control group was included. Therefore, we cannot rule out that the improvement of patients after our programme was only a sign of late CRT effect on remodelling and outcomes. We used a binary definition of CRT response although other authors argue for the concept of 'disease modification' by CRT, with a range of effect.[5] Our study was single centre and numerous biases are inherent to the methodology. In addition, after optimization our rate of patients lost to follow-up was relatively high. Finally, reproducibility of echocardiographic parameters and inter-observer variability was not specifically assessed.

Conclusions

Using a systematic comprehensive clinical and echo-guided CRT optimization, up to one third of initial CRT non-responders experienced CCS improvement at 6 months. However, neither AVd nor VVd echo-guided modification was associated with better clinical outcomes in non-responders. Our study supports the position of last European Society of Cardiology statement, by recommending a close, specialized and multidisciplinary follow-up of these complex patients, without supporting routine use of echo-guided CRT optimization.[5]

Acknowledgements

Conflict of interest

None declared.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Characteristics of patients at optimization time.
Table S2. Data of echo-guided AVd optimization.
Table S3. Data of echo-guided VVd optimization.

References

1. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NAM III, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. 2009; **361**: 1329–1338.
2. Cleland JGF, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005; **352**: 1539–1549.
3. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, Barrabés JA, Boriani G, Braunschweig F, Brignole M, Burri H. 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2021: ehab364.
4. Daubert C, Behar N, Martins RP, Mabo P, Leclercq C. Avoiding non-responders to cardiac resynchronization therapy: A practical guide. *Eur Heart J*. 2017; **38**: 1463–1472.
5. Mullens W, Auricchio A, Martens P, Witte K, Cowie MR, Delgado V, Dickstein K, Linde C, Vernooy K, Leyva F, Bauersachs J, Israel CW, Lund LH, Donal E, Boriani G, Jaarsma T, Berruezo A, Traykov V, Yousef Z, Kalarus Z, Nielsen JC, Steffel J, Vardas P, Coats A, Seferovic P, Edvardsen T, Heidbuchel H, Ruschitzka F, Leclercq C. Optimized implementation of cardiac resynchronization therapy: A call for action for referral and optimization of care. *EP Europace*. 2021; **23**: 1324–1342.
6. Ellenbogen KA, Gold MR, Meyer TE, Fernndez Lozano I, Mittal S, Waggoner AD, Lemke B, Singh JP, Spinale FG, van Eyk J, Whitehill J, Weiner S, Bedi M, Rapkin J, Stein KM. Primary results from the SmartDelay determined AV optimization: A comparison to other AV delay methods used in cardiac resynchronization therapy (SMART-AV) trial: A randomized trial comparing empirical, echocardiography-guided, and algorithmic atrioventricular delay programming in cardiac resynchronization therapy. *Circulation*. 2010; **122**: 2660–2668.
7. Boriani G, Müller CP, Seidl KH, Grove R, Vogt J, Danschel W, Schuchert A, Djiane P, Biffi M, Becker T, Bailleul C, Trappe HJ, Resynchronization for the Hemodynamic Treatment for Heart Failure Management II Investigators. Randomized comparison of simultaneous biventricular stimulation versus optimized interventricular delay in cardiac resynchronization therapy. *Am Heart J*. 2006; **151**: 1050–1058.
8. Steffel J, Rempel H, Breitenstein A, Schmidt S, Namdar M, Krasniqi N, Holzmeister J, Lüscher TF, Ruschitzka F, Hürlimann D. Comprehensive cardiac resynchronization therapy optimization in the real world. *Cardiol J*. 2014; **21**: 316–324.
9. Sinner GJ, Gupta VA, Seratnahaei A, Charnigo RJ, Darrat YH, Elayi SC, Leung SW, Sorrell VL. Atrioventricular dyssynchrony from empiric device settings is common in cardiac resynchronization therapy and adversely impacts left ventricular morphology and function. *Echocardiography*. 2017; **34**: 496–503.
10. Mullens W, Grimm RA, Verga T, Dresing T, Starling RC, Wilkoff BL, Tang WHW. Insights from a cardiac resynchronization optimization clinic as part of a heart failure disease management program. *J Am Coll Cardiol*. 2009; **53**: 765–773.
11. Martin DO, Lemke B, Birnie D, Krum H, Lee KLF, Aonuma K, Gasparini M, Starling RC, Milasinovic G, Rogers T, Sambelashvili A, Gorcsan J 3rd, Houmsse M, Adaptive CRT Study Investigators. Investigation of a novel algorithm for synchronized left-ventricular pacing and ambulatory optimization of cardiac resynchronization therapy: Results of the adaptive CRT trial. *Heart Rhythm*. 2012; **9**: 1807–1814.e1.
12. Brugada J, Delnoy PP, Brachmann J, Reynolds D, Padeletti L, Noelker G, Kantipudi C, Rubin Lopez JM, Dichtl W, Borri-Brunetto A, Verhees L, Ritter P, Singh JP, RESPOND CRT Investigators. Contractility sensor-guided optimization of cardiac resynchronization therapy: Results from the RESPOND-CRT trial. *Eur Heart J*. 2017; **38**: 730–738.
13. Gorcsan J, Abraham T, Agler DA, Bax JJ, Derumeaux G, Grimm RA, Martin R, Steinberg JS, Sutton MSJ, Yu C-M, American Society of Echocardiography Dyssynchrony Writing Group. Echocardiography for cardiac resynchronization therapy: Recommendations for performance and reporting--a report from the American Society of Echocardiography Dyssynchrony writing group endorsed by the Heart Rhythm Society. *J Am Soc Echocardiogr*. 2008; **21**: 191–213.
14. Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. *J Card Fail*. 2001; **7**: 176–182.
15. Varma N, Boehmer J, Bhargava K, Yoo D, Leonelli F, Costanzo M, Saxena A, Sun L, Gold MR, Singh J, Gill J, Auricchio A. Evaluation, management, and outcomes of patients poorly responsive to cardiac resynchronization device therapy. *J Am Coll Cardiol*. 2019; **74**: 2588–2603.
16. León AR, Abraham WT, Brozena S, Daubert JP, Fisher WG, Gurley JC, Liang CS, Wong G, InSync III Clinical Study Investigators. Cardiac resynchronization with sequential biventricular pacing for the treatment of moderate-to-severe heart failure. *J Am Coll Cardiol*. 2005; **46**: 2298–2304.
17. Sogaard P, Egeblad H, Pedersen AK, Kim WY, Kristensen BØ, Hansen PS, Mortensen PT. Sequential versus simultaneous biventricular resynchronization for severe heart failure: Evaluation by tissue Doppler imaging. *Circulation*. 2002; **106**: 2078–2084.
18. Weiss R, Malik M, Dinerman J, Lee L, Petrutiu S, Khoo M. VV optimization in cardiac resynchronization therapy non-responders: RESPONSE-HF trial results. *Heart Rhythm*. 2010; **7**: S26.
19. Valzania C, Biffi M, Martignani C, Diemberger I, Bertini M, Ziacchi M, Bacchi L, Rocchi G, Rapezzi C, Branzi A, Boriani G. Cardiac resynchronization therapy: Variations in Echo-guided optimized atrioventricular and interventricular delays during follow-up. *Echocardiography*. 2007; **24**: 933–939.